UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,006	07/10/2000	Mark A. Schena	M-9216 US	9156

7590 06/05/2003

Gladys H. Monroy
Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, CA 94304-1018

EXAMINER	
FORMAN, BETTY J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,006	SCHENA, MARK A.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *May '03* . 24OCT'03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This action is in response to papers filed 5 May 2003 in which claims 28, 31, 36, 44 and 46 were amended and a Supplemental Information Disclosure Statement and a Declaration filed under 37 C.F.R. 1.131 were submitted. All of the amendments have been thoroughly reviewed and entered.

The previous rejections in the Office Action dated 4 March 2003 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(e) are withdrawn in view of the Declaration of Mark Schena.

The previous rejections under 35 U.S.C. 103(a) are maintained. All of the arguments have been thoroughly reviewed. The arguments regarding the maintained rejections are discussed below. The argument regarding the withdrawn rejections have been considered but are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection. New grounds for rejection are discussed.

Claims 28-46 are under prosecution.

Information Disclosure Statement

2. The references listed on the 1449 received 5 May 2003 have been reviewed and considered. A copy of the signed 1449 is enclosed with this action. Additionally, the International Search Report submitted 5 May 2003 has been reviewed. However, references cited on the search report but not listed on the 1449 have not been reviewed or considered.

While reviewing the application file, it was noted that the 1449 filed 12 September 2000 was not correctly initialed and signed. A copy of the correctly initialed and signed 1449 is included with this action.

Declaration under 37 CFR 1.131

3. The Declaration under 37 CFR 1.131 filed 5 May 2003 is sufficient to overcome the Fan et al reference.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 28-34, 36-39, 41-42 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Shuber (U.S. Patent No. 5,834,181, issued 10 November 1998).

Regarding Claim 28, Shuber discloses a method of simultaneously genotyping multiple samples in a single round of hybridization comprising: incubating a microarray of polynucleotide samples from multiples individuals with a probe mixture of oligonucleotides of known sequence wherein the microarray contains a plurality of samples containing genotypes

of interest with each sample in a distinct location (e.g. Column 13, lines 55-63; Example 2 and Fig. 14) each sample has polynucleotides with a defined segment containing a marker selected from a marker for a gene and markers for one or more allelic variants of the gene, the oligonucleotides in the probe mixture consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which the genotype is to be determined wherein the oligonucleotides complementary to the polynucleotides are selected from those with sequences complementary to a segment containing the marker for a gene, one or more allelic variants of the gene and the gene and one or more allelic variants of the gene (Columns 15-19) the incubating forms hybrids of polynucleotides of the array and complementary oligonucleotides (Column 20, lines 16-44)and allows discrimination at a single nucleotide resolution (i.e. detects point mutations, Column 15, lines 32-33) and detecting stable hybrids formed during the incubation wherein the formation of a hybrid after a single round of hybridization is indicative of a genotype (i.e. allele-specific identification, Example 2).

It is noted that following identification of the hybrid, Shuber sequences the identified hybrids. The instant claims are drawn to a method "comprising" the steps of incubating and detecting. Any additional steps performed in the method of Shuber are encompassed by the open claim language "comprising". Therefore, Shuber discloses the method as claimed.

Regarding Claim 29, Shuber discloses the method wherein the polynucleotide samples of the microarray are amplification products (Column 15-18, Tables 1-8).

Regarding Claim 30, Shuber discloses the method wherein the amplification products are produced by a PCR method (Column 12, lines 22-47 and Example 2).

Regarding Claim 31, Shuber discloses the method wherein the plurality of sample is at least 10 (Column 13, lines 55-61 and Example 2).

Regarding Claim 32, Shuber discloses the method wherein an allele is associated with a disease (e.g. cystic fibrosis, Example 2, Column 18, line 53-Column 19, line 55).

Regarding Claim 33, Shuber discloses the method wherein the disease is a human disease (e.g. cystic fibrosis, Example 2, Column 18, line 53-Column 19, line 55).

Regarding Claim 34, Shuber discloses the method wherein the disease is selected from the group consisting of β-globin, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), and Galactose-! -phosphate Uridyltransferase (Gal-1-PU) (Column 14, lines 44-51.

Regarding Claim 36, Shuber discloses the method wherein the probe mixture comprises oligonucleotides with ten different sequences (Column 18, line 53-Column 19, line 55).

Regarding Claim 37, Shuber discloses the method wherein the oligonucleotides in the mixture are between about 10 and 30 nucleotides in length (i.e. 17-mers, Example 2, Column 18, line 53-Column 19, line 55).

Regarding Claim 38, Shuber discloses the method wherein the distinct segment is between about 40 and 1000 nucleotides (Column 12, lines 30-37).

Regarding Claim 39, Shuber discloses the method wherein incubating is in an aqueous solution comprising salts and detergent (e.g. EDTA & SDS, Column 20, lines 17-22).

Regarding Claim 41, Shuber discloses the method wherein the oligonucleotides of known sequence are labeled (Column 20, lines 1-15).

Regarding Claim 42, Shuber discloses the method wherein the label is fluorescent (Column 25, lines 11-24).

Regarding Claim 46, Fan et al disclose the method wherein the individual is human (Example 2).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 35 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (U.S. Patent No. 5,834,181, issued 10 November 1998) in view of Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997).

Regarding Claim 35, Shuber discloses a method of simultaneously genotyping multiple samples in a single round of hybridization comprising: incubating a microarray of polynucleotide samples from multiples individuals with a probe mixture of oligonucleotides of known sequence wherein the microarray contains a plurality of samples containing genotypes of interest with each sample in a distinct location (e.g. Column 13, lines 55-63; Example 2 and Fig. 14) each sample has polynucleotides with a defined segment containing a marker selected from a marker for a gene and markers for one or more allelic variants of the gene, the oligonucleotides in the probe mixture consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which the genotype is to be determined wherein the oligonucleotides complementary to the polynucleotides are selected from those with sequences complementary to a segment containing the marker for a gene, one or more allelic variants of the gene and the gene and one or more allelic variants of the gene (Columns 15-19) the incubating forms hybrids of polynucleotides of the array and complementary oligonucleotides (Column 20, lines 16-44)and allows discrimination at a single nucleotide resolution (i.e. detects point mutations, Column 15, lines 32-33) and detecting stable hybrids formed during the

incubation wherein the formation of a hybrid after a single round of hybridization is indicative of a genotype (i.e. allele-specific identification, Example 2) wherein the surface comprises at least 1000 locations (Fig. 14) but they are silent regarding the density being 1000 locations/ cm^2 . However, array densities of 1000 locations/cm^2 were well known in the art at the time the instant invention was made as taught by Drmanac. Drmanac teaches a similar method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with probes of a known sequence wherein the array contains a plurality of sample containing genotypes of interest with each sample in a distinct location wherein the microarray comprises at least 1000 locations/cm^2 i.e. 25/mm^2 (Column 5, lines 46-48).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the location density of Drmanac to the microarray of Shuber to thereby maximize the number of assays per hybridization as desired by Shuber (Column 5, lines 21-30). It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 43, Shuber teaches the method where in the allele-specific genetic alterations are identified but they do not specifically teach that the method distinguishes homozygotes and heterzygotes. However, distinguishing between homozygotes and heterzygotes was well known and routinely practiced in the art at the time the claimed invention was made as taught by Drmanac who specifically teaches that samples from homozygotes and heterozygotes are distinguishable (Column 4, lines 7-19). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of Shuber to distinguishing between homozygotes and heterozygotes as taught by Drmanac based on the importance of their distinction as taught by Drmanac (Column 4, lines 7-19).

Regarding Claim 44, Shuber teaches the method wherein the plurality of samples is at least 500 (Column 5,lines 21-30) but they do not teach the samples are at least 5000. However, immobilized sample of at least 5000 were well known and routinely practiced in the art at the time the claimed invention was made as taught by Drmanac who teaches the plurality of samples is at least 5000 i.e. a subarray contains 256 samples (Column 4, lines 42-43) and the array comprises 50 subarrays (Column 3, lines 33-36).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the sample number of Drmanac to the immobilized samples of Shuber to thereby maximize the number of assays per hybridization as desired by Shuber (Column 5, lines 21-30). It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 45, Shuber teaches the method wherein the samples are prenatal blood samples (Column 6, lines 13-19) but they do not specifically teach the blood samples are neonatal.

However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the diagnostic array comprising prenatal blood samples taught by Shuber to comprise samples from neonatal blood for the obvious benefits of prenatal diagnosis i.e. by detecting the presence of mutant genes in neonatal samples, the disease maybe prevented and/or treated as early as possible.

8. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (U.S. Patent No. 5,834,181, issued 10 November 1998) in view of Hames et al (Nucleic Acid Hybridization: a practical approach, IRL Press, Washington DC, 1985, pages 105-108).

Regarding Claim 40, Shuber teaches the method of simultaneously genotyping multiple samples in a single round of hybridization comprising: incubating a microarray of polynucleotide samples from multiples individuals with a probe mixture of oligonucleotides of known sequence wherein the microarray contains a plurality of samples containing genotypes of interest with each sample in a distinct location each sample has polynucleotides with a defined segment containing a marker selected from a marker for a gene and markers for one or more allelic variants of the gene, the oligonucleotides in the probe mixture consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which the genotype is to be determined wherein the oligonucleotides complementary to the polynucleotides are selected from those with sequences complementary to a segment containing the marker for a gene, one or more allelic variants of the gene and the gene and one or more allelic variants of the gene (Columns 15-19) the incubating forms hybrids of polynucleotides of the array and complementary oligonucleotides (Column 20, lines 16-44)and allows discrimination at a single nucleotide resolution (i.e. detects point mutations, Column 15, lines 32-33) and detecting stable hybrids formed during the incubation wherein the formation of a hybrid after a single round of hybridization is indicative of a genotype (i.e. allele-specific identification, Example 2) hybridization is performed below melting of stable hybrids (Column 20, lines 35-40) but is silent regarding hybridizing at about 10° C below stable hybrid melting temperature.

However it was well known in the art at the time the claimed invention was made that stable hybrids of closely related sequences are hybridized and distinguishable at about 10° C below melting temperature as taught by Hames et al (page 105 (i) and page 108, first full paragraph, lines 8-10). It would have been obvious to one of ordinary skill in the art at the

time the claimed invention was made to apply the hybridization temperatures taught by Hames et al (i.e. about 10° C below melting) to the allele-specific hybridizations of Shuber because the hybridizations are designed to distinguish between closely related sequences. Therefore, one of ordinary skill in the art would have been motivated to hybridize the nucleic acids of Shuber at about 10° C below melting for the obvious benefits of distinguishing between their closely related sequences as taught by Hames et al and to thereby accurately genotype the individuals.

9. Claims 28-39 and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997) in view of Brown et al (U.S. Patent No. 5,807,522, filed 7 June 1995).

Regarding Claim 28, Drmanac teaches a method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with probes of a known sequence wherein the array contains a plurality of sample containing genotypes of interest with each sample in a distinct location each sample has polynucleotides with a defined segment containing a marker selected from a gene or markers for one or more allelic variants of the gene, the probes consist essentially of oligonucleotides of known sequence and length and having sequences specifically complementary to those within the defined segments for each sample for which a genotype is to be determined wherein the oligonucleotides are selected from those complementary to the gene and/or one or more allelic variants of the gene, the incubating form hybrids of arrayed polynucleotides and

complementary oligonucleotides and allows discrimination at a single nucleotide resolution and detecting stable hybrids form during the incubation wherein hybrid formation is indicative of a genotype (Example 3, Column 5, line 37-Column 6, line 3 and Example 6, Column 7, line 25-Column 8, line 46). Drmanac teaches the method comprising multiple rounds of hybridization wherein e.g. a round hybridizes with positive probes and a subsequence round hybridizes with negative probes (Column 7,lines 30-61) but Drmanac does not teach detection of the hybrid following a single round of hybridization is indicative of a genotype. However, genotyping comprising a single round of hybridization was well known in the art at the time the claimed invention was made as taught by Brown et al. Brown et al. teach a similar method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with a probe mixture wherein the microarray contains a plurality of samples containing genotypes of interest (amplified region of interest), each sample had polynucleotides with a defined segment containing a marker (region of interest) and the probes consist of oligonucleotides complementary to the regions of interest, the incubating form hybrids and allows discrimination at a single nucleotide resolution (i.e. perfect match) and detecting stable hybrids following a single round of hybridization which is indicative of genotype (Column 15, lines 19-52). Brown et al further teach that their method wherein differentially labeled probes detected following a single hybridization permits simultaneous detection of the plurality of samples with "significant time and cost savings" (Column 15, lines 13-16, 39-43 and 52-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the differentially labeled probes of Brown et al to the method of Drmanac and to differentially label their marker-specific probes to thereby permit simultaneous detection of multiple samples following a single hybridization step for the expected benefits of significantly saving time and money as taught by Brown et al (Column 15, lines 13-16, 39-43 and 52-67).

Regarding Claim 29, Drmanac teaches the method wherein the samples are amplification products (Column 5, lines 30-35).

Regarding Claim 30, Drmanac teaches the method wherein the amplification products are produced by PCR (Column 5, lines 30-35).

Regarding Claim 31, Drmanac teaches the method wherein the plurality of samples is at least 10 i.e. a subarray contains a sample from each of 64 patients (Column 5, lines 59-60).

Regarding Claim 32, Drmanac teaches the method wherein an allele of the gene is associated with a disease (Column 2, lines 5-12 and Examples 6-8, Column 7, line 25-Column 10, line 21).

Regarding Claim 33, Drmanac teaches the method wherein the disease is human disease (Column 2, lines 5-12 and Examples 6-8, Column 7, line 25-Column 10, line 21).

Regarding Claim 34, Drmanac teaches the method wherein the samples are diagnostically important (Column 2, lines 7-12) but they do not teach specific genetic loci. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the genetic diagnostic microarrays of Drmanac to provide specific genetic loci e.g. β-globin, CFTR and GALT, to thereby provide microarrays for disease-specific diagnosis for the expected benefit of rapid diagnosis of clinically important diseases as taught by Brown et al. (Column 15, lines 59-67).

Regarding Claim 35, Drmanac teaches the method wherein the microarray is on a surface comprising at least 1000 locations/cm^2 i.e. 25/mm^2 (Column 5, lines 46-48).

Regarding Claim 36, Drmanac teaches the method wherein the mixture of oligonucleotides comprises at least 10 different sequences i.e. 5 positive for one allele, 5 for another allele and 2 negative (Column 7, lines 29-33).

Regarding Claim 37, Drmanac teaches the method wherein the oligonucleotides are between about 10 and 30 nucleotides in length (Column 4, line 59-Column 5, line 4).

Regarding Claim 38, Drmanac teaches the method wherein the distinct segment is between about 40 and about 1000 nucleotides in length (Column3, lines 27-34).

Regarding Claim 39, Drmanac teaches the method wherein the incubating is in an aqueous solution comprising salt and detergent (Column 18, lines 17-30).

Regarding Claim 41, Drmanac teaches the method wherein the oligonucleotides are labeled (Column 5, lines 5-13).

Regarding Claim 42, Drmanac teaches the method wherein the label is fluorescent (Column 5, lines 5-13).

Regarding Claim 43, Drmanac teaches the method wherein samples from homozygotes and heterozygotes are distinguishable (Column 4, lines 7-19).

Regarding Claim 44, Drmanac teaches the method wherein the plurality of samples is at least 5000 i.e. a subarray contains 256 samples (Column 4, lines 42-43) and the array comprises 50 subarrays (Column 3, lines 33-36).

Regarding Claim 45, Drmanac teaches a method of simultaneously genotyping multiple samples (Example 6, Column 7, line 25-Column 8, line 46) wherein the samples are diagnostically important (Column 2, lines 7-12) but they do not teach the samples are neonatal blood samples. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the diagnostic array comprising mutated genes as taught by Drmanac to comprise multiple forms of genes from neonatal blood samples for the obvious benefits of prenatal diagnosis i.e. by detecting the presence of mutant genes in neonatal samples, the disease maybe prevented and/or treated as early as possible.

Regarding Claim 46, Drmanac teaches the method wherein the mammal is a human (Column 8, lines 52-62).

Response to Arguments

10. Applicant argues that Drmanac and Brown et al do not establish a prima facie case of obviousness because they do not teach every element of the claims. Applicant argues that

Drmanac does not teach detection of hybrid following a single round of hybridization to identify a genotype. The argument has been considered but is not relevant to the instant rejection because Brown et al teaches this element of the claimed invention.

Applicant further argues that the Drmanac's universal set of probes teaches away from the instantly claimed oligonucleotide mixture "consisting essentially of" thereby excluding oligonucleotides not specified in the claim. The argument has been considered however, the MPEP provide guidance when interpreting claims reciting "consisting essentially of".

> For the purposes of searching for and applying prior art absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 (MPEP 2111.03)

Therefore, the claim language "consisting essentially of is interpreted as being equivalent to "comprising" and therefore, encompassing the additional oligonucleotides of Drmanac.

Applicant further argues that Drmanac does not teach the claimed oligonucleotide mixture i.e. oligonucleotides complementary to the polynucleotides are selected from those with sequences complementary to a segment containing the marker for (1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene, and also consisting essentially of optionally, control oligonucleotides. The argument has been considered but is not found persuasive because Drmanac, as Applicant acknowledges, teaches a universal probe set comprising **all 4096 6-mers**, **or all 16,384 7-mers** (Column 4, lines 60-65). A probes set comprising all n-mers comprises oligonucleotides complementary to any sequence. As such, Drmanac's probes meet the limitations of the claims.

Applicant argues that Brown et al teach multiple rounds of hybridization and not the single round as instantly claimed because they teach multiple microarrays on a single substrate and, Applicant asserts, hybridization on the multiple-microarray substrate is multiple rounds of hybridization. The argument has been considered but is not found

persuasive because nowhere does Brown et al teach exposing the multiple microarray to more than one round of hybridization. The fact that multiple microarrays are on a single substrate does not negate the fact that the substrate is hybridized with the oligonucleotide mixture **one time** for a single round of hybridization. Furthermore, the fact that each microarray (within its silicone barrier) on the substrate is hybridized with the oligonucleotide mixture does not negate the fact that that the substrate, and each microarray on the substrate, is hybridized **one time** for a single round of hybridization. Therefore, Brown et al teaches a single round of hybridization as claimed.

Applicant further argues that Brown et al do not teach the claimed oligonucleotide mixture i.e. oligonucleotides complementary to the polynucleotides are selected from those with sequences complementary to a segment containing the marker for (1) a gene, (2) one or more allelic variants of the gene, and (3) a gene and one or more allelic variants of the gene, and also consisting essentially of optionally, control oligonucleotides. The argument has been considered but is not found persuasive because, as discussed above, Drmanac teaches this element of the claims. Furthermore, as Applicant notes, Brown et al specifically teach the immobilized DNA is hybridized with a mutated allele or genetic marker (i.e. known sequence). Applicant appears to be arguing that Brown hybridizes with a "different" allele or marker and therefore does not hybridize with multiple different alleles or markers. However, the instant claims are drawn to a probe mixture. The claims are not limited to a plurality of probes having different sequence. Therefore, an argument regarding the probes of Brown et al not being different is not relevant to the instant claims.

Applicant points to a teaching of Brown wherein it is stated that the microarrays are probes with unknown sequences. The citation is noted, but the single passage does not negate the fact that Brown specifically teach the immobilized DNA is hybridized with a mutated allele or genetic marker (i.e. known sequence) (Column 15, lines 44-47).

Applicant argues that neither Brown et al nor Drmanac teach or suggest the combination of their teachings. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

11. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997) in view of Brown et al (U.S. Patent No. 5,807,522, filed 7 June 1995) as applied to Claim 28 above and further in view of Hames et al (Nucleic Acid Hybridization: a practical approach, IRL Press, Washington DC, 1985, pages 105-108).

Regarding Claim 40, Drmanac teaches a method of simultaneously genotyping multiple samples comprising: incubating a microarray of polynucleotide samples from multiple individuals with probes of a known sequence wherein the array contains a plurality of sample (Column 7, line 25-Column 10, line 21) and Brown et al teach the similar method wherein stable hybrids are detected following a single round of hybridization and the detection is indicative of genotype (Column 15, lines 19-52). Drmanac and Brown et al are silent regarding hybridizing at about 10° C below stable hybrid melting temperature. However it was well known in the art at the time the claimed invention was made that stable hybrids of closely

related sequences are hybridized and distinguishable at about 10° C below melting temperature as taught by Hames et al (page 105 (i) and page 108, first full paragraph, lines 8-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the hybridization temperatures taught by Hames et al (i.e. about 10° C below melting) to the allele-specific hybridizations of Drmanac and Brown et al because their hybridizations are designed to distinguish between closely related sequences. Therefore, one of ordinary skill in the art would have been motivated to hybridize the nucleic acids of Drmanac and Brown et al at about 10° C below melting for the obvious benefits of distinguishing between their closely related sequences as taught by Hames et al and to thereby accurately genotype the individuals.

Response to Arguments

12. Applicant argues that because Brown et al and Drmanac do not teach every element of Claim 28, the combination of Hames et al, Brown et al and Drmanac cannot teach every element of Claim 40. The argument has been considered but is not found persuasive because, as stated above, Brown et al and Drmanac do teach the elements of Claim 28.

13. Applicant's Information Disclosure Statement necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
June 3, 2003